

adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971).

There is no *in haec verba* written description requirement. See MPEP § 2163(I)(B). While support for a claim must be found in the originally filed disclosure, such support may be in the form of express, implicit or inherent support. See MPEP § 2163.05.

The Federal Circuit has held that information that is conventional or well known to one of ordinary skill in the art need not be described in detail in the specification. See *Hybritech v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986). Thus, it logically follows that the absence of definitions or details for well-established terms or procedures cannot be the basis of a proper written description rejection under section 112, paragraph 1. Similarly, the mere inclusion of dictionary or art-recognized definitions known at the time an application is filed, is not considered new matter. See MPEP § 2163.07.

Further, disclosure of one species may adequately represent a genus for written description purposes. This point of law is clearly illustrated in *In re Herschler*, 200 USPQ 711, 714 (CCPA 1979), where disclosure of corticosteroid in DMSO was held to be sufficient to support claims drawn to a method of using a mixture of a “physiologically active steroid” and DMSO because “use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds.” See also, *Rasmussen*, 211 USPQ 323, 326-27 (CCPA 1981) (holding sufficient written description for claims drawn to general methods of “adheringly applying” layers, where disclosure consisted of a single method of adheringly applying one layer to another, since one skilled in the art would understand that it is unimportant how the layers are adhered, so long as they are adhered).

In the instant case, support for the claim phrase “chemotherapeutic stress stimulus” can be found throughout the specification. The Examiner’s attention is directed to the following passages of the specification: page 1, line 10; page 3, line 19; page 4, line 13; page 14, line 22; and page 38, line 7, where “chemotherapeutic agent-induced apoptosis”, “chemotherapeutic therapies” and “chemotherapeutic agents” are all discussed. Clearly, the specification provides explicit support for “chemotherapeutic” and implicit support for “chemotherapeutic stress stimulus” as used in the claims. In light of the written description standard explicated above, Applicants respectfully submit that, at the time of the invention, a

person of skill in the art would have recognized that chemotherapeutic stress stimuli well known in the art fall within the disclosure.

Furthermore, information contained in any part of the disclosure (*i.e.* the specification, the claims or drawings of an application) may be added to any other part of the application without introducing new matter. MPEP § 2163.06. Thus, since support for chemotherapeutic types of stress stimuli exists in the specification, introduction of that limitation into the claims does not represent new matter.

The meaning of chemotherapeutic stress stimulus was well known in the art as of July 26, 1996, the effective filing date of this application. In support of this fact, Applicants are providing herewith a copy of the following reference: Dennis A. Casciato and Barry B. Lowitz, *Manual of Clinical Oncology*, Chapter 4 entitled “*Cancer Chemotherapeutic Agents*” pp. 33-75 (1995) (**Reference CJ**). Therein, Casciato and Lowitz enumerate and categorize numerous chemotherapeutic agents which were well known in the art in 1995, well before the effective filing date of the instant application. Thus, the absence of a detailed itemization of chemotherapeutic stress stimuli cannot serve as a basis for a written description rejection. Such information was well known in the art. In view of the foregoing, reconsideration and withdrawal of this rejection is respectfully requested.

#### **THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH**

Claim 9 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Specifically, the Examiner alleged that the use of the word “meiosis” in Claim 9 is indefinite and ambiguous. Applicants have amended Claim 9 to comply with Examiner’s suggestion and to recite “zeiosis” and not “meiosis.” Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

#### **THE REJECTION UNDER 35 U.S.C. § 103(a)**

The Examiner rejected Claims 1-3, 5, 7 and 9-13 under 35 U.S.C. § 103(a), citing the following six references: (1) Lowe, S.W., *et al.*, 1993, *Cell* 74:957-67 (“*Lowe*”); (2) Jarvis *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91:73-77 (“*Jarvis*”); (3) Cifone, M. G. *et al.*, 1995, *EMBO J.* 14: 5859-68 (“*Cifone*”); (4) Schuchman *et al.*, 1998, U.S. Pat. No. 5,773,278, entitled “Acid Shingomyelinase Gene,” issued June 30, 1998, filed May 3, 1991 (“*Schuchman*”); (5) Horinouchi, K., *et al.*, 1995, *Nature Genetics* 10: 288-93 (“*Horinouchi*”);

and (6) Otterbach, B., et al., 1995, *Cell* 81:1053-61 (“*Otterbach*”). More particularly, the Examiner based the rejection on *Lowe* in view of *Jarvis* and *Cifone* and either *Schuchman* or *Horinouchi* or *Otterbach*.

In response, Applicants respectfully traverse the rejection. None of the cited references, either alone or in combination, teach or suggest the invention as defined in the claims now pending for the reasons specifically set forth below.

### **THE LEGAL STANDARD**

The cited rejections fail to meet the legal standard for holding claims to be obvious under 35 U.S.C. § 103 and should be withdrawn. The objective standard for obviousness was set forth by the Supreme Court of the United States in *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Under *Graham*, an Examiner must make the following preliminary factual determinations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; and (3) the differences between the claimed subject matter and the prior art. Secondary considerations, such as commercial success or long-felt need, must then be considered, if they exist. The obviousness or non-obviousness of the claimed subject matter is determined in light of these inquiries.

For a claim to be obvious in light of the above factual findings, an Examiner must be able to conclude the following about the prior art: (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to those of ordinary skill in the art, to modify the reference or to combine the reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claim limitations.

The Federal Circuit has elaborated on when a suggestion or motivation to combine prior art references exists. Specifically, while the motivation to combine need not be explicitly found in the references considered, a *prima facie* case of obviousness requires proof that the references contain some clear and particular motivation to combine. See *Winner Int’l Royalty Corp v. Wang*, 53 U.S.P.Q.2d 1580, 1586-87 (Fed. Cir. 2000) (upholding validity of claims for lack of suggestion to combine asserted references stating, “Although a reference need not expressly teach that the disclosure contained therein should be combined with another, combinability, in whatever form, must nevertheless be ‘clear and particular’.”); see also MPEP § 2143.01.

The Federal Circuit has also held that the prior art must either expressly disclose every claim limitation or suggest modifications to meet every claim limitation. *Litton Indus. Products, Inc. v. Solid State Systems*, 755 F.2d 158, 164 (Fed. Cir. 1985); see also *In re Royka*, 180 USPQ 580 (CCPA 1974) (holding that all claim limitations must be taught or suggested by the prior art to establish a *prima facie* case of obviousness) (emphasis added). Furthermore, "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

### **THE REFERENCES**

Applicants respectfully submit that the Examiner has misunderstood and/or mischaracterized the teachings of many of the references cited in the March 12, 2002 Office action, in addition to misunderstanding the definition of chemotherapeutic stress stimulus.

Specifically, the Examiner states in the March 12, 2002 Office action that:

*Lowe et al.* teaches a method for identifying compound which increases or decreases a cell's sensitivity to p53-mediated apoptosis comprising contacting p53 deficient cells (p53<sup>-/-</sup>) and p53 positive cells (p53<sup>+/-</sup> and p53<sup>+/+</sup>) with a test compound such as chemotherapeutic agents 5-fluorouracil, etoposide, adriamycin, and sodium azide to induce apoptosis wherein the apoptotic morphology comprises cellular condensation, nuclear condensation or zeiosis.

(March 12, 2002 Office action at 4, internal citations to *Lowe* omitted).

*Lowe* teaches that an oncogene, specifically the adenovirus E1A gene, can sensitize fibroblasts to apoptosis induced by ionizing radiation, 5-fluorouracil, etoposide and adriamycin. Also, *Lowe* discloses that the sensitivity of chemotherapeutic regimens may be accentuated by the inappropriate expression of oncogenes.

*Lowe* does not teach methods to identify any compounds, must less methods to identify compounds that increase or decrease a cell's sensitivity to acid sphingomyelinase-related apoptosis. Moreover, Applicant's respectfully disagree with the Examiner's characterization of 5-fluorouracil, etoposide, adriamycin, and sodium azide as "test compounds". The first three above-named compounds are chemotherapeutic stress stimuli, not test compounds. Sodium azide is an electron transport poison, used in *Lowe* to determine whether coexpression of p53 with E1A made cells sensitive to any toxic treatment, regardless of whether the proposed p53 apoptotic mechanism was involved. Further, the above

mentioned chemotherapeutic agents did not increase or decrease a cell's sensitivity to p53-mediated apoptosis, the chemotherapeutic agents simply induced p53-mediated apoptosis. Counter to Examiner's interpretation, *Lowe* demonstrated that p53, not any "test compounds" sensitized cells to chemotherapeutic stress stimuli.

*Jarvis* is similarly mischaracterized in the March 12, 2002 Office action. The Examiner states, "Jarvis *et al* teach when cells such as HL60 and U937 exhibiting acid sphingomyelinase activity are exposed to various chemotherapeutics stress such as sphingomyelinase and C<sub>8</sub>ceramide, the cells undergo apoptosis." (March 12, 2002 Office action at 5, internal citations to *Jarvis* omitted).

Again, Applicant's respectfully disagree with the Examiner conception of chemotherapeutic stress stimulus. Sphingomyelinase and C<sub>8</sub>ceramide are not chemotherapeutic stress stimuli, and *Jarvis* does not teach that they are. *Jarvis* teaches that exposure of TNF $\alpha$  resulted in internucleosomal cleavage of genomic DNA. *Jarvis* also teaches that neutral sphingomyelinase and synthetic ceramides selectively induce apoptosis. Importantly, *Jarvis* does not teach the role of acid sphingomyelinase in the sphingomyelin pathway examined therein. Only the role of neutral sphingomyelinase (SMase) is discussed. *Jarvis* at 73.

Further, Applicant's respectfully object to the Examiner's characterization of the teachings of *Cifone*. "Cifone *et al* teach when cells such as HuT78 that exhibits [*sic*] acid sphingomyelinase activity are exposed to chemotherapeutics [*sic*] stress stimulus such as crosslinking Fas receptor using anti-Fas antibody or TNF, apoptotic death results." Additionally, the Examiner states that "Cifone *et al* teach that it is of interest to screen for compound which increase or decrease the cell's sensitivity to acid sphingomyelinase related apoptosis such as measuring the levels of ceramide and sphingomyelinase activity." (March 12, 2002 Office action at 6, internal citations to *Cifone* omitted).

Applicant's disagree with Examiner contention that "linking Fas receptor using anti-Fas antibody or TNF" constitute "chemotherapeutic stress stimulus." (March 12, 2002 Office action at 6). *Cifone* does not teach or suggest the above definition of chemotherapeutic stress stimulus. *Cifone* merely discloses a model signaling pathway for the Fas/APO-1 (CD95) receptor. See *Cifone* p. 5865, Figure 8.

Additionally, the "Biological Implications" section of *Cifone* speculates that although "tumour- or virus-transformed cells are likely to develop strategies to block

Fas/APO-1-generated apoptotic signals, unraveling key steps of the Fas/APO-1 apoptotic pathway, should indicate possible targets for these strategies and provide suggestions on how to counteract them.” Cifone at 5865. *Cifone* however, does not suggest the methods of the claimed invention. More specifically, *Cifone* makes no mention of identifying compounds which increase or decrease stress-induced apoptosis. Indeed, *Cifone* makes no mention of chemotherapeutic stress-induced apoptosis at all.

*Schuchman* discloses the full length acid sphingomyelinase sequence and methods of producing transgenic mice that may serve as models for Niemann-Pick Disease in humans. Schuchman also teaches that “modifications may be engineered into the ASM enzyme to produce a more active or stable protein, more enzyme protein, or even change the catalytic specificity of the enzyme.” However, compound identification methods are not taught in the *Schuchman* disclosure. Contrary to the Examiner’s assertion, *Schuchman* does not disclose methods of “screening compounds for treatment of Niemann-Pick disease.” (March 12, 2002 Office action at 6). The Examiner points to no part of the *Schuchman* disclosure for compound screening methods. Specifically, *Schuchman* does not teach or suggest a method for identifying compounds that modulate acid sphingomyelinase-related apoptosis by exposing certain cells to a chemotherapeutic stress stimulus, as recited in all pending claims.

*Horinouchi* teaches acid sphingomyelinase (“ASM”) deficient mice as a model for Niemann-Pick disease types A and B. *Horinouchi* postulates that the ASM deficient mice might be of value in investigating the pathogenesis and treatment of Niemann-Pick disease, and for investigations into the role of ASM in signal transduction and apoptosis. *Horinouchi* at 288. However, *Horinouchi* does not teach or suggest a method for identifying compounds that modulate acid sphingomyelinase-related apoptosis by exposing certain cells to a chemotherapeutic stress stimulus, as recited in all pending claims.

Similarly, *Otterbach* teaches how to produce transgenic ASM deficient mice. Additionally, *Otterbach* theorizes that the ASM deficient mice might facilitate studies on the function of ASM in the generation of ceramide as proposed second messenger in the intracellular signaling pathways and across the plasma membrane. *Otterbach* at 1053. *Otterbach* does not teach or suggest a method for identifying compounds that modulate acid sphingomyelinase-related apoptosis by exposing certain cells to a chemotherapeutic stress stimulus, as recited in all pending claims.

In the present situation, in construing the cited references, the Examiner has failed to present a *prima facie* case of obviousness. The March 12, 2002 Office action does not provide a "clear and particular" motivation to combine the references cited therein. See *Winner*, 53 U.S.P.Q.2d 1580. Furthermore, even if combined, the resulting combination simply does not have the suggestions, much less the teachings, alleged by the Examiner. More specifically, the cited references, even if combinable, do not teach all of the limitations of the pending claims. They do not teach a method for identifying compounds that modulate acid sphingomyelinase-related apoptosis by exposing certain cells to a chemotherapeutic stress stimulus.

In view of the foregoing, Applicants submit that this rejection has been obviated or overcome. Reconsideration and withdrawal are respectfully requested.

#### **CONCLUSION**

Applicants respectfully request entry and consideration of the foregoing amendments and remarks. An early allowance is earnestly sought.

Respectfully submitted,

Date June 12, 2002

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Enclosures



## **EXHIBIT A**

**Attorney Docket No. 6923-106**

**U.S. Application No. 09/928,872**

**Marked-Up Version of the Paragraph Amended in the Specification**

**June 12, 2002**

On page 1, line 1, please insert the following paragraph:

The instant application is a continuation of U.S. Patent App. No. 08/687,707, filed May 26, 1996, which issued as Patent No. 6,274,309, on August 14, 2001.



## **EXHIBIT B**

**Attorney Docket No. 6923-106**

**U.S. Application No. 09/928,872**

**Marked-Up Version of the Amended Claim**

**June 12, 2002**

9. The method of Claim 1 or 10 wherein the apoptotic morphology comprises cellular condensation, nuclear condensation or [meiosis] zeiosis.



## EXHIBIT C

Attorney Docket No. 6923-106

U.S. Application No. 09/928,872

**Claims as Pending Following Entry of Amendments Made Herein**

**June 12, 2002**

1. A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:
  - (a) contacting an acid sphingomyelinase-deficient cell with a test compound;
  - (b) exposing the cell to a chemotherapeutic stress stimulus for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity;
  - (c) exposing an acid sphingomyelinase-deficient cell, in the absence of the test compound, to the chemotherapeutic stress stimulus for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity; and
  - (d) monitoring the exposed cells of steps (b) and (c) for the presence of an apoptotic morphology,such that if the cell from step (b) exhibits a more severe apoptotic morphology, than that of the cell from step (c) the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.
  
2. A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:
  - (a) contacting an acid sphingomyelinase-deficient cell with a test compound;
  - (b) exposing the cell to a chemotherapeutic stress stimulus;
  - (c) exposing an acid sphingomyelinase-deficient cell, in the absence of the test compound, to the chemotherapeutic stress stimulus; and

- (d) comparing the levels of sphingomyelin and ceramide present in the exposed cell of step (b) to the levels present in the exposed cell of step (c),

such that if the level of sphingomyelin in the cell of step (b) is less than that of the cell of step (c), or the level of ceramide in the cell of step (b) is greater than that of the cell in step (c), the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

3. The method of Claim 1 or 2 wherein the acid sphingomyelinase-deficient cell is part of a genetically engineered nonhuman animal deficient for the acid sphingomyelinase gene.

5. A method for identifying a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

- (a) contacting a cell exhibiting acid sphingomyelinase activity with a test compound;
- (b) exposing the cell to a chemotherapeutic stress stimulus;
- (c) exposing a cell exhibiting acid sphingomyelinase activity to the chemotherapeutic stress stimulus, in the absence of the test compound; and
- (d) comparing the levels of sphingomyelin and ceramide present in the exposed cell of step (b) to the levels present in the exposed cell of step (c),

such that if the level of sphingomyelin in the cell of step (b) is greater than that of the cell of step (c), or the level of ceramide in the cell of step (b) is less than that of the cell in step (c), the test compound represents a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

7. The method of Claim 12 wherein the cell is part of a genetically engineered nonhuman animal deficient in endogenous acid sphingomyelinase gene activity and containing integrated in its cells a functional human acid sphingomyelinase transgene capable of expressing functional human acid sphingomyelinase.

9. The method of Claim 1 or 10 wherein the apoptotic morphology comprises cellular condensation, nuclear condensation or zeiosis.

10. A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

- (a) exposing acid sphingomyelinase-deficient cells, wherein the cells are part of cell lines or a genetically engineered nonhuman animal deficient for the acid sphingomyelinase gene, in the presence or the absence of a test compound, to a chemotherapeutic stress stimulus for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity; and
- (b) monitoring the exposed cells of step (a) for the presence of an apoptotic morphology, such that if the cells treated with the test compound exhibit a more severe apoptotic morphology than that of the cells not treated with the test compound, the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

11. A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

- (a) exposing acid sphingomyelinase-deficient cells, wherein the cells are part of cell lines or a genetically engineered nonhuman animal deficient for the acid sphingomyelinase gene, in the presence or the absence of a test compound, to a chemotherapeutic stress stimulus for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity; and
- (b) comparing the levels of sphingomyelin and ceramide present in cells treated with test compound to cells untreated with the test compound, such that if the level of sphingomyelin in the cells treated with the test compound is less than that of cells not treated with the test compound, or the level of ceramide in cells treated with the test compound is greater than in cells not treated with the test compound, the test

compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

12. A method for identifying a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising,

- (a) exposing transgenic cells, comprised of cells deficient in endogenous acid sphingomyelinase gene activity that contain a functional human acid sphingomyelinase gene capable of expressing functional human acid sphingomyelinase, to a chemotherapeutic stress stimulus in the presence or absence of a test compound; and
- (b) comparing the levels of sphingomyelin and ceramide present in cells treated with test compound to cells not treated with the test compound, such that if the level of sphingomyelin in cells treated with the test compound is greater than in cells not treated with the test compound, or the level of ceramide in cells treated with the test compound is less than that of cells not treated with the test compound, the test compound represents a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

13. A method for identifying a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising,

- (a) exposing cells, wherein the cells are genetically engineered cells that exhibit a greater level of acid sphingomyelinase activity than non-genetically engineered cells of the same type, to a chemotherapeutic stress stimulus in the presence or absence of a test compound; and
- (b) comparing the levels of sphingomyelin and ceramide present in cells treated with the test compound to cells not treated with the test compound, such that if the level of sphingomyelin in cells treated with the test compound is greater than in cells not treated with the test compound, or the level of ceramide in cells treated with the test compound is less than that of cells not treated with test compound, the

test compound represents a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis.